Acquired Aplastic Anemia

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KEY CONCEPTS

- Acquired aplastic anemia (AA) is a rare disorder that may be rapidly fatal if left untreated.
- Diagnosis is confirmed by demonstration of peripheral blood pancytopenia and bone marrow aplasia.
- Inherited bone marrow failure should be excluded by specific tests because the management differs.
- Support with red blood and platelet transfusions may be required.
- Bone marrow transplant from an HLA-identical sibling is the treatment of choice for severe and very severe AA, and is curative in more than 75% of cases.
- For patients who lack a sibling donor and for those with moderate AA who are transfusion-dependent, immunosuppression with antithymocyte globulin and cyclosporine^{Rx} is the first line of therapy, resulting in greater than 50% long-term survival.

Aplastic anemia (AA) is a rare disorder, characterized by peripheral blood pancytopenia and a hypocellular bone marrow. Other causes of pancytopenia, such as hypersplenism, marrow infiltration by premalignant or malignant cells (myelodysplastic syndrome [MDS], leukemia, or metastatic cancer), infection (e.g., tuberculosis), or collagen vascular disease must be ruled out. Approximately 75% of patients with AA have the acquired form (Box 1, and see chapter entitled "Inherited Forms of Aplastic Anemia"). Factors implicated in the development of acquired AA include radiation, drugs and chemicals, viruses, toxins, and autoimmune disorders. However, in the majority of cases, no specific cause can be identified; these are termed *idiopathic*. A genetic predisposition may exist that increases the likelihood of bone marrow failure after an environmental insult. Approximately 5% to 10% of cases occur following an episode of hepatitis in which no known viral pathogen or drug has been identified. The reported incidence of acquired AA is two per million per year in Europe and North America, and the incidence is two to three times higher in East Asia.

Aplastic anemia is defined by the presence of bone marrow hypoplasia plus at least two of the following cytopenias:

1. Hemoglobin less than 10 g/dL
2. Platelet count less than 50×10^9/L
3. Neutrophil count less than 1.5×10^9/L

The disease varies from moderate AA (MAA) to severe AA (SAA) based on the severity of pancytopenia (Table 1). Patients with SAA who have a neutrophil count of less than 0.2×10^9/L are considered to have very severe AA (VSAA). The assessment of disease severity is important for treatment decisions and has prognostic significance. Patients with bi- or trilineage cytopenias that do not meet the criteria listed previously are not classified as AA. However, they should have their blood counts monitored because of the risk that they will develop AA.

Bone marrow failure in AA results from an immune-mediated destruction of hematopoietic progenitors. Clinical evidence for this includes circulating cytotoxic lymphocytes and an increased production of cytokines such as γ-interferon and tumor necrosis factor.

BOX 1 Classification of Aplastic Anemia

Acquired Aplastic Anemia

Secondary Aplastic Anemia

- Radiation
- Drugs and chemicals
  - Regular effects: cytotoxic agents, benzene
  - Idiosyncratic reactions: Chloramphenicol^{Rx}
- Viruses
  - Epstein-Barr virus (infectious mononucleosis)

  - Hepatitis without an identified virus
  - Human immunodeficiency (HIV)
- Immune diseases
  - Eosinophilic fasciitis
  - Hypoimmunoglobulinemia
  - Thymoma and thymic carcinoma
  - Graft-versus-host disease (GvHD)
- Paroxysmal nocturnal hemoglobinuria
- Pregnancy

Idiopathic Aplastic Anemia

- Nonsteroidal antiinflammatory drugs
- Antiepileptics, gold, other drugs and chemicals

Inherited Aplastic Anemia

- Fanconi anemia
- Dyskeratosis congenita
- Shwachman-Diamond syndrome
- Amegakaryocytic thrombocytopenia
- Reticular dysgenesis
- Familial aplastic anemias
- Preleukemia (e.g., monosomy 7)
- Nonhematologic syndromes (Down, Dubowitz, Seckel)

Adapted from Young NS, Alter BP: Aplastic Anemia: Acquired and Inherited. Philadelphia: WB Saunders, 1994, p 9.

Table 240-1. Definition of Aplastic Anemia

Category	Definitions
Aplastic anemia (AA)	Hypocellular bone marrow and at least two of: 1. Hemoglobin <10 g/dL 2. Platelets <50 × 10^9/L 3. Neutrophils <1.5 × 10^9/L
Severe AA (SAA)	Hypocellular bone marrow with cellularity <25% or with <30% hematopoietic cells and at least two of: 1. Neutrophils <0.5 × 10^9/L 2. Platelets <20 × 10^9/L 3. Reticulocytes <40 × 10^9/L
Very severe AA (VSAA)	SAA with neutrophils <0.2 × 10^9/L
Moderate AA (MAA)	Moderate cytopenias and hypocellular bone marrow not meeting the criteria for SAA

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Clinical manifestations are related to the severity and duration of the underlying pancytopenia. Early symptoms often include easy bruising and/or mucosal hemorrhage caused by thrombocytopenia. Anemia may lead to fatigue and reduced activity. Infection is a less frequent presentation. However, in the presence of severe neutropenia, fever, mouth sores, and even life-threatening infections can develop rapidly. Lymphadenopathy and hepatosplenomegaly are uncommon and suggest other underlying causes. A preceding history of jaundice may indicate hepatitis-associated AA. A careful history for exposure to drugs, chemicals, and pesticides in the

preceding 6 months should be obtained in all cases.

Expert Opinion on Management Issues

BOX 2 Laboratory Tests Recommended for the Diagnosis of Aplastic Anemia

- Complete blood count, differential, and peripheral smear morphology
- Reticulocyte count
- Hemoglobin F %
- Bone marrow aspirate, biopsy, and cytogenetics
- Peripheral blood chromosome breakage study to exclude Fanconi anemia
- Flow cytometry for CD55 and CD59 to exclude PNH
- Vitamin B_{12} and folate levels
- Liver function tests
- Viral studies: hepatitis A, B, C; EBV; CMV; HIV
- Tests for collagen vascular diseases (e.g. antinuclear antibody and anti-ds DNA)
- Chest x-ray
- Abdominal ultrasound scan

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; PNH, paroxysmal nocturnal hemoglobinuria.

Modified from Marsh JC, Ball SE, Darbyshire P, et al., on behalf of the British Committee for Standards in Haematology: Guidelines for the diagnosis and management of acquired aplastic anaemia. Br J Haematol 123:783, 2003.

Investigations required to confirm the diagnosis of acquired AA and to exclude other possible causes of pancytopenia are listed in Box 2. The complete blood count often reveals a low platelet, hemoglobin, and neutrophil count, although in early stages only thrombocytopenia may be seen. Anemia may be macrocytic or normocytic, and the absolute reticulocyte count is low. Fetal hemoglobin may be high, suggesting "stress hematopoiesis." Serum transaminase levels may be elevated in hepatitis-associated AA. Serology testing for hepatitis A, B, and C, cytomegalovirus (CMV), Epstein-Barr virus (EBV, parvovirus B19, and human immunodeficiency virus (HIV) is indicated to investigate known viral causes. Paroxysmal nocturnal hemoglobinuria (PNH) should be excluded by flow cytometry; phosphatidylinositol glycan (PIG) anchored proteins such as CD55 and CD59 are deficient in PNH. Iron, vitamin B_{12}, and folate levels should be measured to exclude nutrient deficiencies. Specific inherited bone marrow syndromes such as Fanconi anemia must be ruled out (see the chapter "Inherited Forms of Aplastic Anemia"). Bone marrow examination should include both aspiration (for morphology) and biopsy (for cellularity). In AA the bone marrow is hypocellular, with prominent fat spaces and reduced hematopoietic cells with or without an apparent increase in lymphocytes and plasma cells. Dysplastic or immature cells may indicate MDS or leukemia. Cytogenetic analysis should be performed to look for abnormal clones consistent with those diagnoses.

The treatment of AA involves supportive care to prevent complications of pancytopenia and specific therapy aimed at curing the disease. The choice of therapy depends on the severity of the disease and the availability of a matched sibling bone marrow donor (Figure 1). Although spontaneous recovery may rarely occur, definitive treatment should be initiated as soon as possible to reduce the risk of infection, hemorrhage, and alloimmunization.

Supportive care with platelet transfusions is given to maintain the platelet count above 10×10^9/L to prevent life-threatening intracranial or gastrointestinal hemorrhages. Packed red blood cell transfusions should be used if the hemoglobin is below 8 g/dL. Directed donor transfusions from family members should be avoided, and all blood products should be irradiated and leukodepleted to reduce the risk of sensitization to minor histocompatibility antigens. The risk of bacterial and fungal infections (particularly aspergillosis) is proportional to the degree and duration of neutropenia. Bacterial, fungal, and *Pneumocystis* prophylaxis may be used according to institutional guidelines. All infections should be promptly treated with the appropriate systemic antimicrobials.

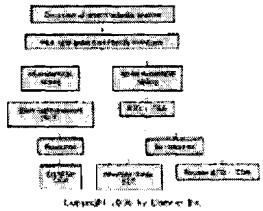

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Figure 1 Treatment algorithm for severe acquired aplastic anemia. ATG, antithymocyte globulin; CSA, cyclosporine® A; HLA, human leukocyte antigen; SCT, stem cell transplant.

Bone marrow transplantation (BMT) from a matched sibling donor is the treatment of choice for pediatric patients, and offers a greater than 75% probability of cure. HLA typing should be done on the patient, parents, and all siblings at the time of diagnosis to identify a possible donor. Current conditioning regimens use immunoablative and non-radiation-based therapy. The standard protocol includes cyclophosphamide®, 50 mg/kg per day × 4 days, in combination with antithymocyte globulin (ATG), 30 mg/kg/day × 3 days. Graft-versus-host disease (GvHD) prophylaxis includes cyclosporine® A (CSA) and methotrexate. The main risks associated with BMT include graft failure in 5% to 10% of patients and GvHD in approximately 25% of patients. Older patient age and exposure to large numbers of blood transfusions may be risk factors for graft failure. The increased intensity of pretransplant conditioning regimens and a slower tapering of post-transplant immunosuppression have been associated with reduced graft rejection. Although a lower incidence and less severe GvHD are seen in children than in adults, mortality from GvHD continues to be a problem. Newer transplant regimens aimed at further intensifying the pretransplant and post-transplant immunosuppression are currently being explored.

Immunosuppressive therapy (IST) is indicated for the approximately 75% of patients with severe or very severe AA who do not have an HLA-matched sibling donor and for patients with moderate AA who are transfusion-dependent. IST with ATG (either horse or rabbit) and cyclosporine® with or without granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) is associated with response rates of approximately 80%, with current 5-year survival rates of approximately 75%. Responses usually occur within the first 3 months. Although most patients show improved blood counts and become transfusion independent, complete normalization of peripheral blood and bone marrow is rarely achieved. Relapses occur in up to 30% of patients. With longer duration of use and slower tapering of cyclosporine®, the relapse rate may be reduced. Side effects from ATG include anaphylaxis, urticaria, fever, chills, thrombocytopenia, and serum sickness. Corticosteroids are usually given along with ATG to reduce these side effects. Cyclosporine® may cause renal dysfunction, hypomagnesemia, hypertension, and neurotoxicity. There is an up to 40% risk of late clonal bone marrow diseases including acute myeloid leukemia (AML), MDS (5%-10%), or PNH (10%-15%) after IST. For patients who fail to respond to IST or relapse after treatment, matched unrelated donor BMT, or further courses of immunosuppression remain treatment options.

Other treatment regimens, including the use of high-dose steroids and androgens, have been tried in the past without much success. Treatment with ATG or cyclosporine® alone is inferior to the combination of the two drugs. Immunosuppression with cyclophosphamide® alone is associated with high mortality caused by prolonged and persistent neutropenia.

Common Pitfalls

Every effort should be made to exclude inherited causes of bone marrow failure before the institution of specific treatment, as failure to diagnose these syndromes may result in death as a result of an ineffective treatment. Delay in treatment of AA increases the risk of death from hemorrhage or infection, and treatment with BMT or IST in the presence of serious infection or uncontrolled bleeding is associated with high mortality. Only irradiated and leukocyte-reduced blood products should be used to avoid sensitization. Cytomegalovirus (CMV)-negative patients should not receive CMV-positive blood products because of the risk of transmission of the virus.

Androgens, lithium®, or isolated use of high-dose steroids should be avoided as primary treatment modalities because these have no beneficial hematological responses in acquired AA. Likewise, the use of growth factors such as G-CSF, GM-CSF, and erythropoietin as single modality treatment should be discouraged.

Communication and Counseling

Aplastic anemia is a rare disease. Treatment is very intensive and is generally instituted in a specialized center that may be far away from the patient's primary residence. The patient and the family should be made aware of the chronic nature of the disease, prolonged treatment, slow recovery, and risks of relapse and late clonal disorders such as MDS, leukemia, and PNH.

Education and emotional and psychological support for the patient and the family are of great importance. The Aplastic Anemia & MDS International Foundation, Inc. (Click here) serves as a resource for patient assistance and emotional support and provides educational materials, family support conferences, and updated medical information.

SUGGESTED READINGS

1. Marsh JC, Ball SE, Darbyshire P, et al., on behalf of the British Committee for Standards in Haematology: Guidelines for the diagnosis and management of acquired aplastic anaemia. Br J Haematol 123:782-801, 2003. **Recommendations of a committee of experts.** Medline Similar articles Full article

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3. Young NS, Alter BP: Aplastic Anemia Acquired and Inherited. Philadelphia: WB Saunders, 1994. **Comprehensive review of acquired and inherited aplastic anemias.**

4. Young NS: Acquired aplastic anemia. Ann Intern Med 136:534-546, 2002. **Describes mechanisms of immune-mediated marrow failure and current treatments.** Medline Similar articles Full article

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